Medical and Pediatric Oncology 29:553–559 (1997)

Feasibility of Sequential High-Dose Chemotherapy and Peripheral Blood Stem Cell Support for Pediatric Central Nervous System Malignancies

Regina I. Jakacki, MD,[1*] Cheryl Jamison,[1] Stephen A. Heifetz,[2] Karen Caldemeyer,[3] Mark Hanna,[4] and Leonard Sender[1]

Background. The outlook for many brain tumors remains poor. Increased dose intensity has been correlated with response rate and survival in many solid tumors.

Patients and Methods. Ten children with recurrent or newly diagnosed brain tumors were treated with four sequential courses of high-dose single agent chemotherapy with peripheral blood stem cell (PBSC) support. PBSC harvesting was undertaken prior to chemotherapy and following the first course of chemotherapy (3.6 g/m^2 etoposide). Each course of chemotherapy consisted of a single drug followed 48 hours later by PBSC reinfusion. Three patients were treated on Regimen A: etoposide, carboplatinum 1.95 g/m^2, cyclophosphamide 5 g/m^2, and thiotepa 300 mg/m^2; three patients were treated on Regimen A′ with carmustine 600 mg/m^2 replacing cyclophosphamide; four patients received Regimen B: etoposide, carboplatinum 1.95g/m^2, cyclophosphamide 7 g/m^2, and thiotepa 900 mg/m^2.

Results. No course of chemotherapy was complicated by >14 days of neutropenia. Platelet recovery was more prolonged, particularly in patients who had previously received craniospinal irradiation. Non-hematologic toxicity was severe with three toxic deaths including two patients who developed hemolytic-uremic syndrome and respiratory failure. Two of three patients with primitive neuroectodermal tumors had a partial response; no responses were observed in patients with high-grade gliomas.

Conclusions. Administration of multiple courses of high-dose chemotherapy with PBSC support is feasible in this patient population and successfully mitigates hematologic toxicity. Non-hematologic toxicity becomes prohibitive as chemotherapy doses are escalated. Med. Pediatr. Oncol. 29:553–559, 1997.

Key words: brain tumors; high-dose chemotherapy; peripheral blood stem cell support

INTRODUCTION

Conventional dose chemotherapy has not significantly altered the bleak outlook for high-grade gliomas and recurrent central nervous system malignancies [1,2]. Several clinical trials involving a variety of solid tumors have shown a correlation between dose intensity (i.e. the amount of drug delivered per unit of time) and both response rate and treatment outcome [3]. The use of peripheral blood stem cells reduces the time to both neutrophil and platelet recovery following chemotherapy administration, allowing dose intensification that cannot be achieved with growth factor support alone [4,5]. We report on the use of peripheral blood stem cells (PBSCs) to allow administration of serial courses of high dose chemotherapy to young patients with recurrent or poor-prognosis malignant brain tumors.

PATIENTS AND METHODS

Patient Selection

Patients with refractory or recurrent primary central nervous system (CNS) malignancies, or previously untreated CNS malignancies felt to have less than a 20% chance of survival with standard therapy, were eligible for treatment if they met the following criteria: age less than 21 years; weight of at least 10 kilograms and adequate renal, liver, cardiac, pulmonary, and bone marrow function. Patients were ineligible if they had received radiation therapy within three months of study entry without biopsy-proven disease. All patients and/or parents signed a written informed consent approved by the Institutional Review Board at the time of study entry.

Chemotherapy administration and follow-up care was

[1]Department of Pediatrics, Division of Pediatric Hematology-Oncology, James Whitcomb Riley Hospital for Children, Indianapolis, IN; [2]Department of Pathology and Laboratory Medicine, Division of Pediatric Pathology, Indiana University Medical Center, Indianapolis, IN; [3]Department of Radiology, Indiana University Medical Center, Indianapolis, IN; [4]Division of Biostatistics, Department of Medicine, Indiana University Medical Center, Indianapolis, IN.

Contract grant sponsor: NCI P01CA59348 grant (RIJ).

Dr. Sender is currently at Children's Hospital of Orange County, Orange County, CA.

*Correspondence to: Regina I. Jakacki, M.D., Section of Pediatric Hematology-Oncology, Riley Hospital for Children, Room 2720, 702 Barnhill Drive, Indianapolis, IN 46202–5225.

Received 30 August 1996; Accepted 7 May 1997

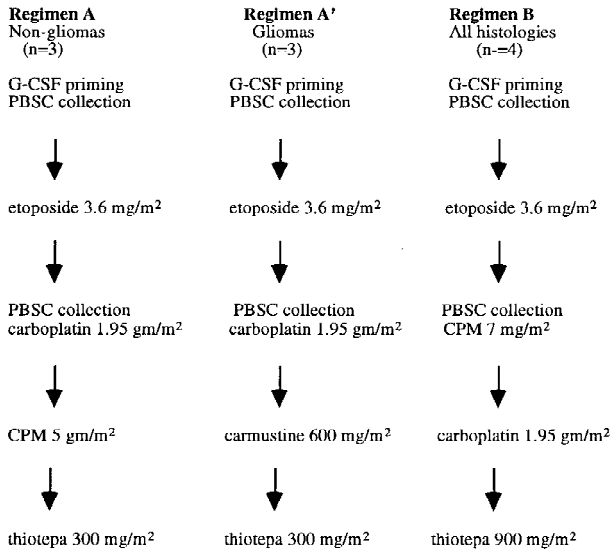

Fig. 1. Schema of therapeutic regimens (A) and (A′) and the dose-escalated regimen (B).

performed at Riley Hospital for Children, Indiana University. Leukapheresis was performed either at Indiana University or Kosair Children's Hospital, University of Louisville.

PBSC Collection and Storage

Leukapheresis was performed through a double-lumen venous dialysis catheter. Peripheral blood stem cells were collected using the Cobe Spectra or the Baxter CS 3000 machine. The machine was primed with irradiated, filtered, packed red blood cells for patients weighing less than 25 kg. PBSCs were divided into aliquots and cryopreserved in 10% dimethyl sulfoxide using controlled-rate freezing and stored at −196 degrees Centigrade.

Treatment Regimen

The treatment schemas are shown in Figure 1. G-CSF was the mobilizer for the initial leukapheresis. The first course of chemotherapy (etoposide) was administered after a minimum of 7×10^8 mononuclear cells (MNC)/kg were harvested. Stem cells were reinfused 48 hours after the completion of the etoposide infusion. Growth factor (10 mcg/kg) was administered daily following the PBSC reinfusion until the ANC recovered to more than 1000/uL and the platelet count stabilized at greater than 30,000/uL without transfusion. The dose of growth factor was increased to 20 mcg/kg/d × 2 days prior to the second leukapheresis. A minimum of 21×10^8 MNC/kg was harvested during the second leukapheresis and divided into three aliquots. In some cases, a third leukapheresis was necessary after the second course of chemotherapy in order to obtain sufficient numbers of cells. Following courses 2–4 (and if no further leukapheresis was needed), growth factor was tapered over two days when the ANC recovered to greater than 2000/uL. Courses 3 and 4 were administered 24 hours after growth factor was discontinued and at least 21 days following the previous course of chemotherapy.

Each course of chemotherapy consisted of a single drug followed 48 hours later by reinfusion of a minimum of 7×10^8 MNC/kg. Etoposide (VP-16) 3600 mg/m^2 was given undiluted by 24-hour continuous infusion. Solumedrol 40 mg/m^2 was given prior to and every eight hours during the etoposide infusion to prevent fever and chills. Carboplatin 650 mg/m^2 was given over 3 hours daily × 3 days (1950 mg/m^2 total dose). Cyclophosphamide (CPM) 2.5 g/m2 × 2 days (5 g/m^2 total dose) was given to patients with non-glioma histologies (Regimen A) while patients with gliomas (n = 3) received carmustine 600 mg/m2 as a continuous infusion over 72 hours (Regimen A′); patients on Regimen B received cyclophosphamide 3.5 g/m2 × 2 days (7 gm/m^2 total dose). Thiotepa 300 mg/m2 over 3 hours was given to patients on Regimen A and A′ and 300 mg/m2/d × 3 days (900 mg/m^2 total dose) was given to patients on Regimen B. Dexamethasone was used only when necessary to control neurologic symptoms.

Further treatment following the last course of chemotherapy was individualized. One patient received additional high-dose chemotherapy with autologous bone marrow rescue. Five patients received involved field external beam radiation therapy. One patient received intracavitary radiolabeled monoclonal antibodies. Survival was determined from the time between the date of study entry and the time of death.

Supportive Care

Chemotherapy administration and PBSC reinfusion followed by 24 hours of intravenous hydration was performed on the inpatient floor. Patients were placed on prophylactic Septra and Fluconazole and those who were seropositive for Herpes simplex were placed on Acyclovir. Transfusions of irradiated, Pall-filtered blood products were used to maintain a hemoglobin above 8.0 gm/dl and platelets above 30,000/mm^3. Patients were hospitalized and placed on broad-spectrum antibiotics for fever above 38.3°C.

Evaluation of Response and Toxicity

Response was evaluated by MRI scans with and without gadolinium prior to the second course of chemotherapy (i.e., following etoposide) and 4 weeks after the last course of chemotherapy. Responses were defined as per the published guidelines for pediatric brain tumors [6].

RESULTS

Patient Characteristics

Ten patients were enrolled on study between August, 1993, and July, 1994. The study was closed in Septem-

TABLE 1. Patient Characteristics

PN	Age/Sex	DX	Location/Extent of disease	Prior therapy	Time from prior therapy	TX regimen	Consolidation
1	8.6/F	Medulloblastoma	Leptomeningeal	CDDP, CPM, VP-16, VCR CARBO, CSXRT	7 mos.	A	—
2	9.3/F	Malignant Glioma	Thalamus	—	—	A′	IF XRT
3	13.1/M	Glioblastoma	Midbrain/Thalamus	CARBO/VCR	1 mo.	A′	IF XRT
4	10.3/M	Gliofibroma	Disseminated	CDDP, VP-16, VCR, IFOSFAMIDE	12 mos.	A	ABMT
5	12.2/M	Glioblastoma	Exophytic Brainstem	IF XRT (FOR CRANIOPHARYNGIOMA)	7.5 yrs	A′	IF XRT
6	3.3/M	PNET	Parietal Lobe	CDDP, VCR, VP-16, CPM, CSXRT	5 mos.	A	Monoclonal Antibody
7	4.0/F	Eppendymoma	Posterior Fossa	CDDP, CPM, VP-16, VCR, CARBO, IF XRT	18 mos.	B	—
8	15.1/M	Anaplastic Astrocytoma	Occipital Lobe	—	—	B	IF XRT
9	12.5/M	Medulloblastoma	Leptomeningeal	CDDP, VP-16, CPM, VCR, CSXRT	4 mos.	B	—
10	11.3/F	Glioblastoma	Thalamus	—	—	B	Surgery/ IF XRT

CDDP = Cis-platin, CPM = cyclophosphamide, VCR = vincristine, Carbo = carboplatin, XRT = radiation therapy, IF = involved field, CS = craniospinal, ABMT = autologous bone marrow transplant.

ber, 1994 because of unacceptable non-hematologic toxicity on Regimen B. The clinical features of the patient population are presented in Table 1. Patients ranged in age from 3–15 years. Five patients had received prior radiation therapy including three who had received craniospinal radiation, two patients had received involved field radiation. One patient had received radiation therapy 7.5 years earlier for a craniopharyngioma. Six patients had received prior chemotherapy, while three patients had received no treatment other than surgery. Patients with localized disease underwent maximal surgical resection, if feasible, prior to study entry. Three patients with disseminated recurrent disease were not reoperated on at the time of recurrence. All patients had radiographic evidence of disease at the time of study entry.

PBSC Collection and Reinfusion

A total of 62 pheresis collections were performed. All procedures were well tolerated and lasted from 3–7 hours each. Three patients required additional stem cell harvesting after the second course of chemotherapy.

The percentage of CD34+ cells obtained per collection was measured in nine of the ten patients. Patients who had *not* received prior craniospinal radiation therapy had a significantly greater increase in the percentage of CD34+ cells harvested on the first day of pheresis after etoposide priming (relative to the percentage harvested on the first day of pheresis following G-CSF priming alone) compared to those patients who had previously undergone craniospinal radiation therapy ($p = 0.028$ by Wilcoxon rank-sum test [7]).

The median number of mononuclear cells/kg reinfused per course was 7.3×10^8 (range $5.4 \times 10^8 - 10.2 \times 10^8$). The number of CD34+ cells/kg reinfused ranged from 0.1×10^6 to 53×10^6, with a median of 2.5×10^6.

Chemotherapy Delivery

Eight patients received the prescribed four courses of chemotherapy. Patient #6 suffered an intracranial hemorrhage secondary to head trauma, three weeks after receiving his third course of chemotherapy (cyclophosphamide). Due to slow neurologic recovery, the fourth course of chemotherapy was not given. Patient #10 did not receive the last course of chemotherapy because of the untoward non-hematologic toxicity seen in the first 3 patients treated on Regimen B. Chemotherapy was delivered a median of 21.5 days apart (range 17–38 days).

Hematologic Recovery

None of the 38 courses of chemotherapy were complicated by more than 14 days of neutropenia (ANC <500). Neutropenia lasted a median of 8 days per course on Regimen A (range 5–14 days), 3.5 days/course on Regimen A′ (range 0–14 days), and 7 days/course (range 3–13 days) on Regimen B. None of the three patients who received carmustine on Regimen A′ developed neutropenia (<500), and two of the three patients did not require a platelet transfusion.

Only five patients (50%) developed thrombocytopenia (<30,000/uL) following 3.6 g/m^2 of etoposide. Thrombocytopenia was more severe following carboplatin, particularly on Regimen B, where three of four patients remained platelet dependent for more than 14 days. Patients who had received prior craniospinal irradiation showed the longest times to platelet recovery. The median number of platelet transfusions/course of chemo-

TABLE II. Toxicity

Days Hospitalized for Toxicity	(Median, Range)
Etoposide	3 (0–7)
Carboplatin	1.5 (0–4)
Cyclophosphamide	2 (0–8)
BCNU	0
Thiotepa	
300 mg/m^2	1 (0–5)
900 mg/m^2	16 (15–54)
Cycles with fever/neutropenia	18/38 (47.4%)
Documented Infections/#Courses	
Positive blood cultures	8/38 (21.1%)
C. Difficile infections	6/38 (15.8%)
Ototoxicity	
Grade 1	3 patients
Grade 2	4 patients
Grade 4	1 patients
Transaminitis (transient)	
VP-16	1/10 patients (Grade 3)
Carboplatin	2/10 patients (Grade 4)
Veno-occlusive disease	
Thiotepa (900 mg/m^2)	1/3 patients (Grade 4)
Mucositis	
Thiotepa (900 mg/m^2)	2/3 patients (Grade 4)
HUS/Pulmonary insufficiency	
Regimen A	1/5[a] patients
Regimen B	1/3[a] patients
Toxic deaths	
Regimen A	1/6 patients
Regimen B	2/4 patients

[a]patients completing entire region

therapy was 3 (range 2–9) on Regimen A and 1.5 (range 0–7) on Regimen A′. On Regimen B, the median platelet transfusions/course was 4 for the regimen as a whole, although patients required a median of 6 units after carboplatin and 9 units after thiotepa.

Five patients received involved field radiation therapy following their last course of chemotherapy. Patient #3 started radiation with a platelet count of 47,000 and required periodic platelet support until his death from tumor progression seven weeks later. Patient #10, who received only three of the four courses of chemotherapy, developed protracted myelosuppression following radiation therapy. Her ANC ranged between 700–1500/uL, platelet counts between 40–60,000/uL, and periodic red cell transfusions were required to maintain her Hb >8.0 g/dl. A back-up aliquot of stem cells was reinfused three months following the completion of radiation therapy with recovery of counts shortly thereafter.

Toxicity

Four of 12 courses (33%) on Regimen A′, 8 of 11 courses (73%) on Regimen A and 6 of 15 courses (40%) on Regimen B were complicated by fever and neutropenia. There was only one episode of bacteremia on Regimen A′ vs three each on Regimens A and B. No patient developed clinical sepsis.

The median number of days hospitalized for toxicity following the first three courses of chemotherapy was brief (median 2 days, range 0–8). However, prolonged hospitalizations were required for all three patients who received the higher dose of thiotepa on Regimen B, two of whom died of toxicity.

Toxic Deaths

There were three toxic deaths. Two patients developed hemolytic-uremic syndrome (HUS) in conjunction with bilateral pulmonary infiltrates and died of respiratory failure despite aggressive ventilatory and pharmacologic support.

Patient #2. Seven weeks after receiving the last course of chemotherapy, the patient complained of severe fatigue, abdominal pain, and dyspnea. Laboratory evaluation revealed a Hb of 6.0 g/dl, wbc 2.8/uL, plts 2,000/uL, blood urea nitrogen 38 mg/dl (nl 5–20 mg/dl), and creatinine 1.2 mg/dl (nl 0.3–0.8 mg/dl). The peripheral blood smear showed schistocytes and a serum haptoglobin was <5 mg/dl (nl 31–209 mg/dl). A urinalysis showed 10–20 rbc/hpf. Following transfusion of packed cells and platelets, she developed respiratory distress and hypertension. A chest X-ray revealed diffuse bilateral pulmonary opacities. Open lung and kidney biopsies were performed. She became increasingly difficult to oxygenate secondary to pulmonary hypertension and expired two days later. Microscopic examination of the lungs at the time of autopsy revealed patchy diffuse alveolar damage with hyaline membrane formation, mild interstitial fibrosis and atypical hyperplastic alveolar lining cells. There was medial hypertrophy and intimal hyperplasia of small pulmonary arteries with occasional microthrombi. The kidneys revealed microthrombi within glomerular capillaries and cortical infarcts, consistent with HUS.

Patient #7. Seven weeks after receiving the last course of chemotherapy, the patient developed thrombocytopenia, hemolytic anemia, hypertension, oliguria, and respiratory distress. Her BUN rose to 139 mg/dl and creatinine to 1.3 mg/dl. She became increasingly difficult to oxygenate despite ventilatory support and expired several days later. Microscopic examination of the lungs at autopsy revealed diffuse alveolar damage with atypical type II pneumocytes and mild interstitial fibrosis. In addition, there were small multi-focal abscesses with fungal hyphal forms consistent with aspergillosis. The kidneys showed changes characteristic of HUS with microthrombi in greater than 90% of the glomerular capillaries and renal cortical arterioles.

Patient #9. Developed fever, abdominal pain, diarrhea, and vomiting four days after receiving his last course of chemotherapy. He subsequently developed a direct hyperbilirubinemia and fluid sensitivity consistent with veno-occlusive disease of the liver. His bilirubin

TABLE III. Response and Survival Data

PN	Diagnosis	Response to VP-16	Response after completion of therapy	Survival (months)	Cause of Death
1	Medulloblastoma	PD	PR	11	Progressive disease
2	Malignant glioma	PD	SD	5	HUS/respiratory failure
3	Glioblastoma	PD	PD	7	Progressive disease
4	Gliofibroma	PR	PR	6	VOD during BMT
5	Glioblastoma	PD	PD	8	Progressive disease
6	PNET	PR	PR	44+	Alive
7	Ependymoma	PD	MR	5	HUS/respiratory failure
8	Anaplastic astrocytoma	SD	PD	9	Progressive disease
9	Medulloblastoma	SD	SD	3	VOD/cerebral edema
10	Glioblastoma	SD	SD	8	Progressive disease

SD = stable disease; MR = minor response; PR = partial response; PD = progressive disease; HUS = hematolytic uremic syndrome; VOD = veno-occlusive disease.

rose to a maximum of 20 mg/dl. He became increasingly confused and intermittently delirious and agitated. Shortly before death he became unresponsive with dilated, nonreactive pupils. A CT scan of the brain revealed cerebral edema. Autopsy showed diffuse cerebral edema and bilateral watershed infarcts. Tumor was found throughout the leptomeninges and brainstem. The liver was enlarged with cholestasis and hemosiderosis. The kidneys and lungs were unremarkable.

An autopsy was also performed in patient #3 who died of progressive disease. The lungs and kidneys showed no changes suggestive of toxicity. Four other patients had follow-up pulmonary function testing performed at the completion of chemotherapy, showing no significant changes compared to the baseline testing.

Tumor Response and Survival

Four patients showed progressive tumor growth and/or neurologic deterioration requiring increased steroids following etoposide (2 glioblastomas, 1 medulloblastoma, 1 ependymoma). Two patients (#4 and #6) had a radiographic response to etoposide.

Two of 3 patients with primitive neuroectodermal tumors showed radiographic improvement by the completion of treatment, whereas there were no objective radiographic responses in any of the five patients with high grade gliomas (three PD, 2 SD).

Three patients died of toxicity directly related to the treatment regimen and a fourth patient died of veno-occlusive disease of the liver following consolidation with further high-dose chemotherapy and autologous bone marrow rescue. One patient with a recurrent supratentorial PNET (#6) remains alive after consolidation with intracavitary monoclonal antibodies.

DISCUSSION

The majority of chemotherapeutic agents show a steep dose-response curve in vitro [8]. Studies have demonstrated a log-linear dose-response effect for alkylating agents, suggesting that even modest increases in drug dose may result in substantial increases in cell-kill [9]. The Goldie-Coldman hypothesis [10] states that as many effective drugs should be used as early in treatment as possible, to minimize the probability of resistance developing in the residual tumor cells. The additive toxicities of multiple drugs however, often limits the ability to substantially dose-escalate each agent, resulting in a trade-off between maximizing the dose-response curve and capitalizing on the additive effects. The lack of ability to dose-escalate is felt to be the reason that results with ''eight-in-one'' chemotherapy were so disappointing [1,11]. By administering four drugs in high-doses, albeit one drug at a time, we hoped to take advantage of the dose-response curve to overcome relative drug resistance, achieve rapid cytoreduction and decrease the risk of emergence of new drug-resistant mutants without losing the benefits of combination therapy. The chemotherapeutic agents in our regimen were chosen because of their efficacy against malignant brain tumors in Phase II studies, the log-linear dose-response data and the non-cell-cycle-dependent cytotoxicity of the platinums and alkylators. In addition, the non-hematologic dose-limiting toxicities for each of the drugs used in our regimen were qualitatively different, e.g. cardiac for cyclophosphamide, mucositis for thiotepa and etoposide, liver and lung damage for carmustine, and liver damage for carboplatin. Multiple organ system failure is typically seen with high-dose combination chemotherapy and usually not when the drugs are employed separately, even when the same total dose of drug is delivered [12]. We had hoped that by giving the drugs sequentially, we would minimize non-hematologic toxicity.

The feasibility of harvesting peripheral blood stem cells in this patient population and using them to successfully support/rescue the marrow after each course of high-dose chemotherapy was clearly demonstrated. There were no unexpected technical difficulties and suf-

ficient numbers of PBSCs were able to be harvested. Hematologic toxicity, particularly neutropenia, was quite tolerable. No patient had more than 14 days of neutropenia and the delayed nadir following carmustine was avoided. Time to recovery of the ANC following 900 mg/m^2 thiotepa was not significantly different from that of patients who received 300 mg/m^2. Although protracted thrombocytopenia following carboplatin or thiotepa was seen in the patients who had received prior craniospinal radiation therapy, it was not unmanageable.

Etoposide has been used to significantly expand and mobilize the pool of circulating hematopoietic progenitor cells in patients receiving chemotherapy [13]. Single agent high-dose etoposide followed by autologous bone marrow rescue resulted in partial responses in three of four patients with recurrent glioblastoma multiforme [14]. Despite our use of even higher doses of etoposide, four of ten patients developed clinical and/or radiographic progression within three weeks. In addition, there was marginal benefit over G-CSF alone in terms of the percentage of CD34+ cells/kg harvested from patients who had previously received craniospinal radiation therapy. The use of cyclophosphamide, which has shown efficacy in a wide variety of CNS malignancies, [15], may have been a better choice for a chemotherapy mobilizer.

Rodenhuis reported dose-limiting non-hematologic toxicity after three courses of high-dose cyclophosphamide, thiotepa, and carboplatin, including two patients who developed HUS [16]. Unfortunately, administering the drugs as single agents sequentially at the doses used in Regimen B, also resulted in unacceptable non-hematologic toxicity. The cause of death in our two patients with HUS was respiratory and post-mortem findings were consistent with a toxic insult to the lungs. Both cyclophosphamide and carmustine can cause pulmonary toxicity [17]. The fact that one patient received cyclophosphamide and the other carmustine supports a cumulative effect of the high-dose chemotherapy rather than a specific causative agent. The extreme toxicity observed in the patients who received 900 mg/m^2 thiotepa, a dose used frequently in autologous BMT regimens without untoward toxicity, further supports a cumulative toxic effect on normal tissue.

Other than the one patient on Regimen A′ who developed the syndrome of HUS and respiratory insufficiency, Regimens A and A′ were extremely well-tolerated from both a hematologic and non-hematologic standpoint. Radiographic responses were seen in the patient with a disseminated gliofibroma and two of three patients with PNETs, one of whom is a long-term survivor. There were no objective responses in the patients with high-grade gliomas, all of whom had bulky residual disease. Such patients are known to have a notoriously bleak outlook and have fared poorly in previous studies with high-dose chemotherapy [18,19]. Whether combination chemotherapy would have resulted in more objective responses is unknown.

In conclusion, harvesting and reinfusion of PBSCs following multiple courses of high-dose chemotherapy is feasible even in heavily pre-treated children with brain tumors, although patients with a history of craniospinal irradiation tend to have more protracted thrombocytopenia and mobilize less well following recovery from myelosuppressive chemotherapy. Hematopoietic toxicity was acceptable and neutropenia following chemotherapy administration was of relatively short duration. The non-hematologic toxicity encountered on the dose-escalated regimen was severe. Radiographic responses and even long-term survival were seen in patients with chemosensitive tumors. Although the objective response rate in patients with high-grade gliomas was disappointing, toxicity was minimal after carmustine with peripheral blood stem cell support. Increasing dose-intensity by decreasing the time interval between chemotherapy courses (e.g. with nitrosoureas) rather than by dose-escalation may reduce non-hematologic toxicity. This approach is currently under investigation.

REFERENCES

1. Finlay JL, Boyett JM, Yates AJ, et al.: Randomized phase III trial in childhood high-grade astrocytoma comparing vincristine, lomustine and prednisone with the eight-drugs-in-1-day regimen. J Clin Oncol 13:112–123, 1995.
2. Jenkin R, Boesel C, Ertel I, et al.: Brainstem tumors in childhood: A prospective randomized trial of irradiation with and without adjuvant CCNU, vincristine, and prednisone. J Neurosurg 66:227–233, 1987.
3. Hryniuk W: The importance of dose intensity in the outcome of chemotherapy, In DeVita V, Hellman S, Rosenberg S (eds): Important Advances in Oncology. Philadelphia, PA, Lippincott, 1989, pp. 121–141.
4. Tepler I, Cannistra SA, Frei E, et al.: Use of peripheral-blood progenitor cells abrogates the myelotoxicity of repetitive outpatient high-dose carboplatin and cyclophosphamide chemotherapy. J Clin Oncol 11:1583–1591, 1993.
5. Shea TC, Mason JR, Storniolo AM, et al.: Sequential cycles of high-dose Carboplatin administered with recombinant human granulocyte-macrophage colony-stimulating factor and repeated infusions of autologous peripheral-blood progenitor cells: a novel and effective method for delivering multiple courses of dose-intensive therapy. J Clin Oncol 10:464–473, 1992.
6. Zeltzer PM, Friedman HS, Norris DG, Ragab AH: Criteria and definitions for response and relapse in children with brain tumors. Cancer 56:1824–1826, 1985.
7. Armitage P, Berry G: Statistical Methods in Medical Research (2nd edition). Oxford, UK, Blackwell Scientific Publications, 1987, pp 412–414.
8. Frei E, Canellos GP: Dose: a critical factor in cancer chemotherapy. Am J Med 69:585–594, 1980.
9. Frei E, Teicher B, Holden S, et al.: Preclinical Studies and Clinical Correlation of the Effect of Alkylating Dose. Cancer Res 48: 6417–6423, 1988.
10. Goldie JH, Coldman AJ: Application of the theoretical models to

chemotherapy protocol design. Cancer Treat Rep 70:127–131, 1986.
11. Boyett J, Zeltzer P, Finlay J, et al.: Progression-free survival and risk factors for primitive neuroectodermal tumors of the posterior fossa in children: Report of the Children's Cancer Group Randomized Trial, CCG-921. Proc Am Soc Clin Oncol 14:283, pg. 147, 1995.
12. Frei E: Pharmacologic strategies for high-dose chemotherapy. In Armitage JO, Antman KH (eds): ''High-Dose Cancer Therapy.'' Baltimore: Williams and Wilkins, 1995, pp. 3–16.
13. Gianni AM, Bregni M, Siena S, et al.: Granulocyte-macrophage colony-stimulating factor or granulocyte colony stimulating factor infusion makes high-dose etoposide a safe outpatient regimen that is effective in lymphoma and myeloma patients. J Clin Oncol 10:1955–1962, 1992.
14. Wolff SN, Fer MF, McKay CM, et al.: High-dose VP-16–213 and autologous bone marrow transplantation for refractory malignancies: A Phase I study. J Clin Oncol 11:701–705, 1983.
15. Lachance DH, Oette D, Schold C, et al.: Dose escalation trial of cyclophosphamide with sargramostim in the treatment of central nervous system neoplasm. Med Pediatr Oncol 24:241–247, 1995.
16. Rodenhuis S, Westermann A, Holtkamp MJ, Nooijen WJ, Baars JW, van der Wall E, Slaper-Cortenbach ICM, Schornagel JH: Feasibility of multiple courses of high-dose cyclophosphamide, thiotepa and carboplatin for breast cancer or germ cell cancer. J Clin Oncol 14:1473–1483, 1996.
17. Twohig KJ, Matthay RA: Pulmonary effects of cytotoxic agents other than bleomycin. Clinics in Chest Medicine 11:31–54, 1990.
18. Heideman RL, Douglass EC, Krance RA, et al.: High-dose chemotherapy and autologous bone marrow rescue followed by interstitial and external-beam radiotherapy in newly diagnosed pediatric malignant gliomas. J Clin Oncol 11(8):1458–1465, 1993.
19. Finlay JL, Goldman S, Wong MC, et al.: Pilot study of high-dose thiotepa and etoposide with autologous bone marrow rescue in children and young adults with recurrent CNS tumors. J Clin Oncol 14:2495–2503, 1996.